Comments on CARC report from Matt Martin (EPA/ORD/NCCT)

Overall, the findings and justifications in the CARC report appear scientifically sound and well-reasoned. However, there is a clear difference in the outcome compared to the IARC review of the carcinogenicity of glyphosate. The IARC report concludes that glyphosate is a Probable Human Carcinogen (Group 2A), the CARC report found that glyphosate is "Not Likely to be Carcinogenic to Humans".

In my opinion, the disparities between IARC and CARC reports is primarily due to differences in the underlying decision context and guidance used by the two groups. The CARC uses the 2005 EPA Cancer Guidelines as compared to the IARC, which uses the 2006 IARC Preamble.

Another contributing factor was the study inclusion criteria. The CARC, in part, relies on study inclusion criteria in the 2012 Guidance for Considering and Using Open Literature Toxicity to Support Human Health Risk Assessment. IARC relies on inclusion criteria in the IARC Preamble to the Monographs. These approaches resulted in critical differences in the underlying data used in these two assessments. I have provided a brief review of these differences below.

The CARC report included, and placed heavy weight on, two published review articles (Greim et al. (2015) and Kier and Kirkland (2013)). These two published review papers cited a number of primary studies that were not available to the IARC. The review papers provided only summary supplemental documents (e.g., 1-2 page summaries for each genotoxicity study). The IARC Working Group, concluded that the supplemental studies did not meet the criteria for data inclusion due to insufficient information to evaluate their reliability. In addition, in the genotoxicity evaluation, the CARC reported that some of the studies used in the IARC evaluation did not meet the Klimisch criteria for reliability and, therefore these studies were not considered by the CARC. It is clear that these two groups did not rely on the same data.

The CARC states, for instance:

> *"The four studies which were negative for carcinogenicity were reported in the review article by Greim et al. (2015) but were not included in the IARC evaluation. This omission of the negative findings from reliable studies may have had a significant bearing on the conclusion drawn for evidence of carcinogenicity in animals."*
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> *"Furthermore, IARC's evaluation did not include a number of negative results from studies that were reported in the review article by Kier and Kirkland (2013). The inclusion of the positive findings from studies with known limitations, the lack of reproducible positive findings and the omission of the negative findings from reliable studies may have had a significant bearing on IARC's conclusion on the genotoxic potential of glyphosate."*

Excerpt from IARC Monograph on Glyphosate:

> *In reference to the Greim et al. (2015), "The Working Group was unable to evaluate these studies, which are not included in Table 3.1 and Section 5.3, because the information provided in the review article and its supplement was insufficient (e.g., information was lacking on statistical methods, choice of doses, body-weight gain, survival data, details of histopathological examination, and/or stability of dosed feed mixture)."*

*In reference to the Kier & Kirkland (2013), "The Working Group determined that the information in the supplement to Kier & Kirkland (2013) did not meet the criteria for data inclusion as laid out in the Preamble to the IARC Monographs, being neither "reports that have been published or accepted for publication in the openly available literature" nor "data from governmental reports that are publicly available" (IARC, 2006). The review article and supplement were not considered further in the evaluation."*

Again, it is clear that the two organizations did not use the same data in their assessments, and this appears to be a contributing factor for the disparity in classifications of glyphosate carcinogenicity. However, if there is any attempt at a reconciliation of these two assessments, I do not believe that using the same data or normalizing the study inclusion criteria would necessarily result in arriving at the same classification due to the inherent differences between the EPA and IARC cancer assessment guidelines.